

**AMENDMENTS****In the Claims**

1.(canceled)

2.(canceled)

3.(canceled)

4.(canceled)

5.(canceled)

6.(canceled)

7.(canceled)

8.(canceled)

9.(canceled)

1 10.(previously presented) A composition comprising a polymerizing agent including a molecular  
2 and/or atomic tag covalently bonded to a site on the polymerizing agent and a monomer including  
3 a molecular and/or atomic tag, where at least one of the tags has a fluorescence property that  
4 undergoes a change before, during and/or after each of a sequence of monomer incorporations due  
5 to an interaction between the polymerizing agent tag and the monomer tag and where the changes  
6 in the detectable property generate data evidencing each monomer incorporation producing a  
7 monomer sequence read out.

1 11.(previously presented) The composition of claim 10, wherein the change in the fluorescence  
2 property results from a change in the conformation of the polymerizing agent from a first  
3 conformational state to a second conformational state and back again during each monomer  
4 incorporation.

1 12.(previously presented) The composition of claim 10, wherein the fluorescence property has  
2 a first detection propensity when the polymerizing agent is in the first conformational state and a  
3 second detection propensity when the polymerizing agent is in the a second conformational state.

1 13.(previously presented) The composition of claim 12, wherein the polymerizing agent is a  
2 polymerase or reverse transcriptase.

Page 2

Response to 3 March 2005 Notice of Non-Compliant Amendment

USSN: 09/901,782 - via Fax: 703 872 9306

ROBERT W. STROZIER, P.L.L.C.

PAGE 3/9 \* RCVD AT 3/11/2005 12:29:23 PM [Eastern Standard Time] \* SVR:USPTO-EFXRF-1/0 \* DNR:8728306 \* CSD:713 541 4968 \* DURATION (mm:ss):03:34

**BEST AVAILABLE COPY**

1 14.(previously presented) The composition of claim 13, wherein the polymerase is selected from  
2 the group consisting of *Taq* DNA polymerase I, T7 DNA polymerase, Sequenase, and the Klenow  
3 fragment from *E. coli* DNA polymerase I.

1 15.(previously presented) The composition of claim 13, wherein the reverse transcriptase  
2 comprises HIV-1 reverse transcriptase.

1 16.(currently amended) The composition of claim 12, wherein each of the monomers  
2 comprises a deoxynucleotide triphosphate (dNTP) and the monomer tag is covalently bonded to the  
3  $\beta$  or  $\gamma$  phosphate group of each dNTP.

1 17.(previously presented) The composition of claim 10, wherein the tags comprise fluorescent  
2 tags and the fluorescence property comprises an intensity and/or frequency of emitted fluorescent  
3 light.

1 18.(currently amended) The composition of claim 17, wherein the fluorescence property is  
2 fluorescence resonance energy transfer (FRET) where either the monomer tag or the polymerase tag  
3 comprises a donor and the other tag comprises an acceptor and where FRET occurs when the two  
4 tags are in close proximity.

5 19.(currently amended) The composition of claim 14, wherein the polymerase comprises *Taq*  
6 DNA polymerase I having a tag attached at a site selected from the group consisting of 513-518,  
7 643, 647, 649 and 653-661 and mixtures or combinations thereof of the *Taq* polymerase, where the  
8 tag comprises a fluorescent molecule.

20.(canceled)

21.(canceled)

22.(canceled)

22.(canceled)

23.(canceled)

24.(canceled)

Page 3

Response to 3 March 2005 Notice of Non-Compliant Amendment  
USSN: 09/901,782 - via Fax: 703 872 9306

ROBERT W. STROZIER, P.L.L.C.

PAGE 4/9 \* RCVD AT 3/11/2005 12:29:23 PM [Eastern Standard Time] \* SVR:USPTO-EFXRF-1/0 \* DNIS:8729306 \* CSID:713 541 4668 \* DURATION (mm:ss):03:34

**BEST AVAILABLE COPY**

25.(withdrawn) A single molecule sequencing apparatus comprising a substrate having a first chamber in which at least one tagged polymerase is confined therein and a second chamber including tagged dNTPs and a channel interconnecting the chambers, where a detectable property of at least one tag undergoes a detectable change during a monomer incorporation cycle.

1 26.(withdrawn) The apparatus of claims 24, further comprising a plurality of monomer  
2 chambers, one for each tagged dNTP.

1 27.(withdrawn) A mutant Taq polymerase comprising native Taq polymerase with a cysteine  
2 residue replacement at a site selected from the group consisting of 513-518, 643, 647, 649 and 653-  
3 661 and mixtures or combinations thereof.

1 28.(withdrawn) The polymerase of claim 27, wherein the cysteine residue includes a tag  
2 covalently bonded thereto through the SH group.

1 29.(withdrawn) A system for retrieving stored information comprising:  
2 a unknown nucleotide sequence representing a data stream;  
3 a single-molecule sequencer including a polymerase having a tag associated therewith and  
4 monomers for the polymerase, each monomer having a tag associated therewith;  
5 an excitation source adapted to excite the at least one of the tags; and  
6 a detector adapted to detect a response from at least one of the tag,  
7 where the response changes during polymerization of a complementary sequence and the  
8 changes in response represent a content of the data stream.

1 30.(withdrawn) A system for determining sequence information from a single molecule  
2 comprising:  
3 a unknown nucleotide sequence;  
4 a single-molecule sequencer comprising a polymerase having a tag associated therewith and  
5 monomers for the polymerase, each monomer having a tag associated therewith;  
6 a excitation source adapted to excite at least one of the tags; and  
7 a detector adapted to detect a response from at least one of the tags,  
8 where the response changes during polymerization of a complementary sequence and the

Page 4

Response to 3 March 2005 Notice of Non-Compliant Amendment

ISSN: 00901.782 - via Fax: 703.872.9306

PAGE 5/9 \* RCVD AT 3/11/2005 12:29:23 PM [Eastern Standard Time] \* SVR:USPTO-EFXRF-1/0 \* DNS:8729306 \* CSD:713 541 4968 \* DURATION (mm-ss):03-34

ROBERT W. STROZIER, P.L.L.C.

**BEST AVAILABLE COPY**

changes in the response represent the identity of each nucleotide in the unknown sequence.

31.(withdrawn) A method for sequencing a molecular sequence comprising:

supplying an unknown sequence of nucleotides or nucleotide analogs to a single-molecule sequencer comprising a polymerase having a fluorescent donor covalently attached thereto and monomers for the polymerase, each monomer having a unique fluorescent acceptor covalently bonded thereto;

exciting the fluorescent donor with a light from an excitation light source;

detecting emitted fluorescent light from the acceptor during a monomer incorporation cycle via a fluorescent light detector, where an intensity and/or frequency of the emitted light for the acceptors changes during each monomer incorporation cycle; and

converting the changes into an identity of each nucleotide or nucleotide analog in the unknown sequence.

32.(withdrawn) A method of sequencing an individual nucleic acid molecule or numerous individual molecules in parallel including the steps of:

immobilizing a member of the replication complex comprising a polymerase including a tag attached thereto, a primer or a template sufficiently spaced apart to allow resolution detection of each complex on a solid support;

incubating the replication complex with cooperatively-tagged nucleotides, each nucleotide including a unique tag at its gamma-phosphate, where each nucleotide can be individually detected;

detecting each nucleotide incorporated by the polymerase as the polymerase transitions between its open and closed form, which causes a change in a detectable property of at least one of the tags or as the pyrophosphate group is released by the polymerase; and

relating the changes in the detectable property to the sequence of nucleotides in an unknown nucleic acid sequence.

33.(withdrawn) A  $\gamma$ -phosphate modified nucleoside comprising  $\gamma$ -phosphate modified dATP, dCTP, dGTP and dTTP.

34.(withdrawn) A primer sequence or portion thereof selected from the group consisting of Sequence 1 through 29.

35.(canceled)

36.(canceled)

37.(canceled)

38.(canceled)

39.(canceled)

40.(canceled)

41.(canceled)

42.(canceled)

43.(canceled)

44.(canceled)

45.(canceled)

46.(canceled)

47.(canceled)

1 48.(new) A composition comprising a polymerizing agent including at least one molecular  
2 and/or atomic tag covalently bonded to a site on the polymerizing agent, where a fluorescence  
3 property of the tags undergoes a change before, during and/or after each of a sequence of monomer  
4 incorporations and where the changes in the fluorescence property generate data evidencing each  
5 monomer incorporation producing a monomer incorporation read out and where the polymerizing  
6 agent comprises a *Taq* DNA polymerase I having a tag covalently bonded to an amino acid site of  
7 the *Taq* polymerase selected from the group consisting of 513-518, 643, 647, 649 and 653-661 and,  
8 where the tag comprises a fluorescent molecule.

1 49.(new) The composition of claim 48, wherein the fluorescence property has a first value  
2 when the polymerizing agent is in a first state and a second value when the polymerizing agent is  
3 in a second state, and where the polymerizing agent changes from the first state to the second state  
4 and back again during each monomer incorporation.